A Tribute to Ronald T. Borchardt — Teacher, Mentor, Scientist, Colleague, Leader, Friend and Family Man

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In reflecting on his extensive career, Ronald T. Borchardt (known to his students, colleagues, friends and family members as "Ron"), who is a Distinguished Professor Emeritus at The University of Kansas-Lawrence (KU), has told many of his friends and colleagues that he would like for them to look back on his accomplishments and know that, in the words of Frank Sinatra, "I did it my way." As this Dedicated Issue of the Journal of Pharmaceutical Sciences reflects on the vast impact Ron has had in several areas of science through his role as teacher, mentor, scientist and collaborator, we should also take the time to reflect on the ways in which the unique culmination of his life's choices have led to these contributions. It is a life marked by distinctive and singular achievements, by personal and public successes, and an instructive demonstration of one who has blazed a trail from humble beginnings in a small town in Central Wisconsin to a very successful career at KU. Ron was not born an exception. However, through his hard work, dedication, and the support of his family and colleagues, he has become an exception, a "Giant in the Pharmaceutical Sciences", by doing it his way.

Early Life and Influences

Born February 18, 1944, in Wausau, WI, Ron came from humble beginnings. His mother (Helen) worked in the lunchroom at a nearby middle school and his father (Martin) worked in a local factory. Although Ron's parents were working class people, with no more than a grade-school education, they encouraged Ron and his older sister Judi (Borchardt) Eckhart to see the value in their education and supported that throughout their lives.

In what may be a surprise to many of Ron's former graduate students, postdoctoral fellows, colleagues and collaborators, his sister recalls that Ron was never a good student, not in elementary, middle or high school. She remembers him as a B-C student whose focus was more on skating at the local ice rink and playing baseball and basketball. However, he was not totally unproductive in his early years. Even as a young man, Ron worked hard to earn his way: e.g., mowing lawns, shoveling snow, delivering newspapers, and landscaping were among the tasks he pursued. It was his summer job at a local factory after graduating from high school that convinced Ron that college may be a better option than the backbreaking labor of loading bags of roofing granules onto rail cars.

Though Ron's focus was often more on sports and work than academics during this period, he learned other valuable lessons pursuing these interests, namely, hard work, collegiality, and mentorship. Though Ron had the heart to be a basketball player, he did not have the talent. His high school basketball coach, Marshall Taylor, found a way to use Ron's talents as a manager of the team that won the 1960 Wisconsin state championship. "Coach Marsh" led by example, providing a role model for the young men on his team, showing them how to be gentlemen. Ron remembers learning from him how to motivate and to provide a positive impact in the lives of young people, a lesson central to his own success as a teacher and mentor at KU.

So, despite the lack of early academic excellence, Ron always embodied many of the qualities that eventually led to his success: an ability to lead others, to control situations, to take in information, and a willingness to work hard.

College Life and an Academic Transition

Even with Coach Marsh's advice to Ron to pursue his "intellectual talents" over pursuing basketball, Ron still took some time to ultimately focus on his academics. A former classmate in the School of Pharmacy at the University of Wisconsin-Madison (UW), Judith Thompson (Clinical Associate Professor-Emeritus at UW) recalls that Ron probably spent his initial semesters of pre-pharmacy at the University of Wisconsin-Marathon County playing too much Bridge and having too much fun outside the classroom. However, after transferring to UW at Madison to begin his studies in the School of Pharmacy, Ron's focus began to change.

Both Ron's sister Judi and his classmate in the School of Pharmacy, Judy Thompson, recall his experience in organic chemistry at UW as the point at which they witnessed a change in the seriousness with which he took his studies. His sister recalls that many of her own friends struggled greatly with organic chemistry. However, Ron "breezed" through this course with great joy. She believes organic chemistry turned Ron around academically and "opened the door to science" for him.

Judy Thompson recalls while many of Ron's classmates in the School of Pharmacy wanted to start small businesses as pharmacists when they graduated, Ron was part of a smaller group in the Class of '67 who focused on earning advanced degrees and pursuing careers in academia or industry in the pharmaceutical sciences. Because the Pharmacy Program at UW was relatively small, about 100 students in a class, peers became more like family in what Judy Thompson calls "an enriched research environment." Judy says that being in Madison really "lit a fire under [Ron]." His focus became tighter, and he became almost like a "heat-seeking missile" with respect to learning new things. Furthermore, because he "learns things to a degree that other people do not," he became very successful in his academics endeavors in the School of Pharmacy at UW.

While Ron's parents placed great emphasis on the education of their children, they did not have the financial means to pay their children's room and board and tuition at UW. Therefore, Ron had to work each step of the way for his undergraduate education. In the School of Pharmacy at UW, Ron found work that would change his career trajectory from becoming a pharmacist to becoming a pharmaceutical scientist. Ron's job involved doing all of "the dirty work" in Professor Morris Kupchan's research laboratory. However, the time that Ron spent doing everything from washing dishes, to collecting plants, to extracting potential anticancer drugs from plants, became pivotal for his decision to pursue a career in science instead of becoming a pharmacist. After working in Professor Kupchan's research laboratory for approximately 2 years, Ron officially became a member of the "Research Team" when Professor Kupchan gave Ron his first research project. This research project ultimately gave raise to Ron's first scientific paper in the Journal of Organic Chemistry.[1]

Judy Thompson also reminds us of another aspect of Ron's early academic life that has advanced throughout his career, his collegiality. She notes that while many students who are at the top of the class often feel overly competitive, sometimes even sabotaging one another's success, Ron was "diametrically opposed" to this behavior. She remembers that if she ever needed any kind of help, he was there. "It didn't matter if I scored better," she recalls. "He was the epitome of a colleague."

As Ron neared the end of his undergraduate education (B.S. degree in Pharmacy, 1967) at UW, he made a key decision to follow the advice of a trusted faculty advisor, which was to contact Professor Edward E. Smissman at KU to discuss graduate studies. Professor Smissman, who was a former faculty member at UW, had moved 5 years earlier to KU to assume a Distinguished Professorship and the Chairmanship of the Department of Medicinal Chemistry.

Ron and his wife, Pamela (Pam), his college sweetheart whom he married in 1966, say they were very impressed by the way Professor Smissman and his wife Clare interacted with graduate students and their academic colleagues during their very first meeting with the Smissmans in December 1966. Even in their early correspondence regarding Ron's application to Graduate School at KU, one can see Professor Smissman's attention to detail, his thoroughness as well as his kindness and generosity in answering each question that Ron posed. Ron ultimately accepted the offer from Kansas and he and Pam moved to Lawrence in June 1967 so Ron could start his graduate studies under the direction of Professor Smissman in Medicinal Chemistry at KU. Professor Smissman's influence on Ron cannot be overstated and, in time, Professor Smissman would become like a second father to Ron.

Graduate Education with Professor Edward E. Smissman

When Ron joined the relatively new research group of Professor Smissman in the Department of Medicinal Chemistry at KU in June 1967, he found that Professor Smissman was establishing a very creative program exploring a novel concept. The program was based on the realization that some drugs are conformationally mobile, i.e., they can with small energetic costs change their molecular shapes among a number of different shapes or "conformers". Such drugs in some cases are known to bind to several different macromolecular targets, chiefly proteins, such as enzymes, receptors, etc., to produce a different pharmacological effect for each such interaction. The hypothesis held that different conformers of the drug – or the natural effector - might be complementary in structure, thus might be a "better fit" for the different targets, and produce in this way a distinct effect with each interaction.

Today such a hypothesis can be and has been explored by determining the structures of the free target protein and of the complexes of the target with the natural effector or a synthetic or natural inhibitor. In the late Sixties, such approaches lay well beyond the technology of the times. Ron therefore used organic chemistry to design and synthesize a series of "conformationally frozen" structures. In these structures, the conformational mobility has been blocked so that only one conformer is possible at ordinary temperatures. In Ron's work, he typically made a series of different synthetic compounds into each of which a different conformer was "frozen." By studying the pharmacological and biochemical results of interaction of the target molecule with each of the "conformationally frozen" molecules, one discovers which conformer "fits" which target molecule. Today, the approach is a general protocol for the application of rational drug design.

Ron's work with Professor Smissman produced his doctoral dissertation entitled "A Stereochemical Approach to the Adrenergic System", which was defended in 1970. From his Ph.D. dissertation, Ron and Professor Smissman derived three papers, which were published in the Journal of Medicinal Chemistry in 1971. In two of these papers,[2,3] Ron described the use of a rigid 10-carbon "platform" (trans-decalin) into which he had built the four

most stable conformers of the neurotransmitters dopamine and nor-epinephrine. These distinct conformers, unable to interchange, were exposed to the catabolic enzyme for the natural compounds, catechol-O-methyltransferase, and each "frozen" conformer had a different rate of metabolism. Still another paper[4] with Professors Smissman and Barbara Schowen described frozen conformers of acetylcholine, the cholinergic neurotransmitter, again with four frozen conformers that reacted at different rates by the acetylcholine catabolic enzyme acetylcholinesterase.

We hope that readers will easily appreciate what a great resonance in the medicinal chemistry world of the late Sixties and early Seventies was evoked by the publication of the papers deriving from Ron's doctoral dissertation. We would suggest that, while acknowledging the importance and recognition of the scientific findings for Ron's fledgling career, his personal interactions with Professor Smissman and his observations of the attitudes and actions of Professor Smissman during his graduate work may also have contributed much of great value for Ron's subsequent and spectacular career. Those readers familiar with Ron's attitudes and practices will readily agree that Ron seems to have interjected Professor Smissman's characteristics, or perhaps they were already there genetically and just fell in with Professor Smissman's traits, smoothly and fortunately. Among these were:

Generosity: It has been said of working with Professor Smissman, the only problem was to keep him from giving all – the entirety – of the credit for the work to his collaborators. We have never known another scientist so creative in attempting to deflect the recognition of his accomplishments onto others. He could make outwitting him in these efforts very difficult.

Transparency and Openness: Professor Smissman took little or no interest in keeping his work secret as he shepherded it into publication. His motto seemed to be "tell everybody everything." This attitude made working with him much simpler than it might otherwise have been.

Broad Scientific Scope: We believe Professor Smissman considered himself an organic chemist with an interest in the medicinal-chemical applications of organic chemistry, and he certainly knew and understood everything that was happening in organic chemistry. But he also knew and understood essentially everything that was afoot in medicinal chemistry, pharmacology, biochemistry, and probably a number of other fields. Whenever a new technique was introduced that seemed at least of borderline interest to his work (protein crystallography, nuclear magnetic resonance, and computational chemical theory), Professor Smissman leapt on it like the outstanding student he once had been. Soon he knew how to make use of it, and was taking steps to fund the purchase of the relevant machinery for use at KU and to obtain positions and funding to add new specialists in the field to the KU faculty.

Postdoctoral Study with Drs. Louis A. Cohen and C.R. Creveling at the National Institutes of Health

As Ron's graduate studies were finishing up, he arranged (with strenuous support from Professor Smissman) to spend a postdoctoral period with Dr. Louis A. Cohen in the Laboratory of Chemistry of the National Institute of Arthritis and Metabolic Diseases (NIAMD, a part of the National Institutes of Health, NIH). Dr. Cohen, a highly respected physical-organic chemist, had recently published the initial paper[5] in his series "Stereopopulation

Control", in which he pointed out that an ingenious arrangement of three methyl groups, the "trimethyl lock," could immobilize certain internal motions of the parent compound, very much related to what Ron had accomplished in a different way in the work reported in his doctoral dissertation (1970) and published three Journal of Medicinal Chemistry papers[2-4] in 1971 and 1972 . Ron held his NIH appointment from 1969 until 1971 and during that time carried out synthetic and kinetic studies on the "trimethyl-lock" approach that were published in five Journal of the American Chemical Society papers[6-10] that appeared in 1972 and 1973.

That Ron's and Dr. Cohen's "trimethyl-lock" publications were truly pioneering is beautifully articulated in a Perspective article published recently by Michael Levine and Ronald Raines.[11] Quoting from the article, Levine and Raines say the following about the "trimethyl lock": "The Trimethyl lock has been employed in chemical, biological and pharmacological contexts, providing exceptional stability of conjugates until initiation of a designated reaction triggers rapid scission. The trimethyl lock is a readily accessible and highly adaptable module. Its conjugation to the amino group of a molecule of interest requires only a condensation reaction, and its trigger can be exchanged to alter spatial or temporal aspects of release. The breadth of its demonstrated utility has been remarkable."[11]

In the process of his pioneering research on the "trimethyl lock" at the NIH, Ron strengthened his skills in measuring and interpreting kinetic data, tools that would later serve him well in his penetration of the fields of prodrugs and the stability of peptides and proteins later in his career.

In his "spare time" at NIH, not commonly thought a concept that applies to a beginning scientific career, Ron taught himself protein chemistry and enzymology including enzyme kinetics, and began his work on catechol-O-methyltransferase, the enzyme used with his decalin derivatives upon which he later achieved international fame, including the work with Dr. C.R. (Bob) Creveling that was published in 1973.[12] Among the several ways that Ron's professional friendship with Dr. Creveling helped bring him into the neuroscientific community as a rising leader was their cooperation in organizing international gatherings and publication of their results.

Professorial Ranks in Biochemistry

Having completed his appointment at NIH in 1971, Ron accepted an appointment as assistant professor of Biochemistry at KU during the same year. His first four single-author papers[13-16] on catechol-O-methyltransferase, along with a paper[17] with Ron's first graduate student and now-Howard Q. Ferguson Distinguished Professor Dhiren Thakker, all appeared in 1973, then another single-author paper on the same subject came out in 1974.[18] The program on transmethylation was launched. By 1975, Ron was an Established Investigator of the American Heart Association and associate professor of Biochemistry at KU, with his reputation beyond KU rapidly expanding. He was awarded a full professorship in 1979, with his publication list numbering into the seventies and a substantial research group pursuing the transmethylation theme. In 1981 Ron was recognized for his further achievements by appointment as Solon E. Summerfield Distinguished Professor of Biochemistry and Medicinal Chemistry.

Transmethylation and S-Adenosyl-L-Homocysteine Hydrolase

Ron's contributions to medicinal chemistry and biochemistry in this area, always supported by thoroughgoing basic enzymology and mechanistic biochemistry, have primarily centered around the design, synthesis and evaluation of inhibitors of S-adenosylmethionine (AdoMet)-dependent methyltransferases, either directly on specific methyltransferases or indirectly through inhibition of adenosyl-homocysteine (AdoHcy) hydrolase. The latter results in elevation of AdoHcy, a common product inhibitor of AdoMet-dependent methyltransferases.

As a new KU faculty member in 1971, Ron designed inhibitors of catecholamine-O-methyltransferase (COMT), establishing structure-activity relationships for certain classes of inhibitors,[13-16,19,20] designing affinity labeling reagents[17,18,21-25] and conducting mechanistic studies.[26-28] COMT is responsible for the metabolism of neurotransmitters norepinephrine, epinephrine, and dopamine. Thus inhibition of this enzyme in vivo could potentiate neuronal activity by elevating synaptic levels of these neurotransmitters.

His work in this area quickly expanded into the design and synthesis of inhibitors of other methyltransferases, including histamine N-methyltransferase,[29-31] indole ethylamine N-methyltransferase,[32] t-RNA methyltransferases,[33] phenylethanolamine N-methyltransferase (PNMT),[34-47] protein carboxyl methytransferase [48-52] and viral mRNA methyltransferases.[53-56] The development of PNMT inhibitors and protein carboxyl methyltransferase arose from fruitful collaborations with fellow KU faculty members Professors Gary Grunewald and Charles O. Rutledge, respectively.

Further expansion into the area of transmethylation resulted from a focus on broad-spectrum inhibition of AdoMet-dependent methyltransferases by AdoHcy analogs, with systematic modifications of the amino acid, sugar and base moieties.[52,57-64] These broad-spectrum methyltransferase inhibitors were found to also block viral mRNA methyltransferases, which are critical for translation of viral proteins in infected cells. Ron's 1980 publication of a Perspective article in the Journal of Medicinal Chemistry on AdoMet-dependent methyltransferases as potential therapeutic targets[65] established him as a broad thinker in this important area of investigation and directly inspired a young graduate student (now-Professor Michael Wolfe) in the Department of Medicinal Chemistry at KU to join Ron's research group to do the research for his Ph.D. dissertation.

Ron's focus then turned toward indirect inhibition of methyltransferases, particularly as potential broad-spectrum antiviral agents, through inhibition of AdoHcy hydrolase. Carbocyclic nucleoside natural products aristeromycin and neplanocin A were shown to be potent inhibitors of AdoHcy hydrolase, and the Borchardt group carried out molecular dissection and other analog designs of these compounds, establishing structure-activity relationships, developing chemical tools for mechanistic understanding, and working toward compounds that retain the broad-spectrum antiviral properties while minimizing cytotoxic effects.[66-111] As one example, Ron's group showed that removal of the 4'-hydroxylmethylene group of neplanocin A retained potent AdoHcy hydrolase inhibition and antiviral activity while reducing cytotoxicity, apparently by preventing conversion to the 5'-triphosphate metabolite, which interacts with other proteins and become incorporated into cellular DNA.[67,88,112]

The many significant advances that were make over the years by Borchardt's research group on the design and synthesis of very potent and very specific inhibitors of AdoHcy hydrolase inhibitors were made possible through long standing and very productive collaborations with Professor Morris J. Robins at Brigham Young University, Professor Stanley Wnuk at Florida International University and Professor Eric DeClerq at the Katholieke Universiteit in Leuven, Belgium.

The Borchardt group also made many seminal contributions to the understanding of the structure and catalytic mechanism of AdoHcy hydrolase.[113-123] The mechanism by which designed adenosine analogs inactivate AdoHcy hydrolase was also elucidated and provided better understanding of the enzyme's active site and catalytic mechanism.[112,119,124-133] These advances were made possible through long standing and productive collaborations with Ron's fellow KU faculty members Professors Richard Schowen and Krzysztof Kuczera, and Professor P. Lynne Howell at the University of Toronto.

More recent efforts in Ron's laboratory have focused on AdoHcy hydrolase from trypanosomes: the cloning and characterization of the enzyme allowed comparative biochemistry and the search for selective inhibitors for the treatment of deadly infection by this parasite.[105,112,119,124-134] Selectivity is currently most likely to emerge not from catalytic-site-directed inhibitors, but instead from cofactor-binding-site-directed inhibitors.[135-137]

The above provides a brief summary and not an in-depth review of Ron's contributions over the past 45 years to the area of AdoMet-dependent transmethylations. For more details about his publications in this area, please refer to the following website: http://pharmchem.ku.edu/ronald-borchardt-0.

The Change to Pharmaceutical Chemistry

In 1983, Professor Takeru Higuchi put aside the role of Chair of the Department of Pharmaceutical Chemistry at KU, continuing his research and entrepreneurial activities as the Regents Distinguished Professor, allowing the department to add a new colleague as Chair. Ron was already the Solon E. Summerfield Distinguished Professor of Biochemistry and Medicinal Chemistry at KU, and he soon joined the Department of Pharmaceutical Chemistry as Chair and Summerfield Professor (1983). Ron has described[138] how his move to Pharmaceutical Chemistry affected his responsibilities in research and graduate education: "… this career change required me to 'phase out' most of the drug discovery-oriented research projects ongoing in my laboratory in 1983 because they had been designed for graduate students and postdoctoral fellows in biochemistry and medicinal chemistry. While I was phasing out productive research projects that had contributed significantly to my early successes in academia, I had to 'phase in' new research projects in the areas of cellular and molecular biopharmaceutics and pharmaceutical biotechnology, which I felt were more suited to the interests of graduate students and postdoctoral fellows with research interests in pharmaceutical chemistry."

Ron has said that "this was a very stimulating time in my life",[139] but also has referred to it as a "great leap of faith" in his career. His approach to drug delivery compared to others working in this field in the mid-to-late 1980s was unique because he looked at the problems as a medicinal chemist with reduction to the cellular and molecular levels. He realized that one major challenge in medicinal chemistry is how to get a drug to its site of action and he wholly exploited this key turning point in his career to expand his personal research interests into

cellular and molecular biopharmaceutics, an area that he felt would become very important to drug discovery scientists as they attempted to "design drugs with ADME (absorption, distribution, metabolism, excretion) in mind."[140]

The evolution of Ron's research interests as a pharmaceutical scientist from the 1980s through the 2010s began by developing and validating practical models for biological barriers. He realized that one major challenge in medicinal chemistry is how to get a drug to its site of action and he felt that such models would become very important to drug discovery scientists as they simultaneously optimized the pharmacological and drug-like properties of lead molecules through rational drug design strategies or by fixing their poor drug-like properties using prodrug design strategies. Consequently, the Borchardt laboratory became users of these cell culture models, as well as traditional in situ models, to elucidate how the structure of peptides and peptidomimetics affected their permeation across the intestinal mucosa and the blood-brain barrier (BBB) and to evaluate novel prodrug strategies for delivering therapeutic peptides orally and into the brain. Such cell-based systems are now used routinely in the pharmaceutical industry to aide design of safer and more efficacious drugs.

Practical Models for Biological Barriers to Drug Delivery

A major output from Ron's research group was the development and use of cell culture models of the intestinal mucosa and the BBB. In a 1997 interview,[139] Ron said that he is "most proud of our accomplishments in biopharmaceutics, particularly in the area of cell culture systems and their use to study drug transport." Ron realized that the pharmaceutical industry needed models to study these two very important barriers that were major hurdles in the delivery and development of efficacious drugs. In the early 1980s, barrier function was studied in animal models or isolated tissues, but these models were expensive, time consuming, and had drawbacks.[141,142] Ron "envisioned these in vitro cell culture models as having significant potential for estimating the oral absorption and the brain permeation of drug candidates, thus reducing the need to conduct expensive and sometime controversial animal experiments".

Ron's new interests in applying cell culture models to the study of drug transport began in early 1984 when now-Dean and Professor Audus joined his research group as a postdoctoral fellow. Ron had developed a particular interest in growing cells on permeable supports that would allow investigation of transcellular transport of drugs. This interest was further fueled by discussions with research groups at The Upjohn Company (Kalamazoo, MI) and INTERx Research Corporation-Merck Sharp and Dohme Research Laboratories (Lawrence, KS) that had similar interests and the financial resources to help pursue specific projects in Ron's laboratory. The first system that the Borchardt group explored was a cell culture model for the BBB. After initial attempts to establish cultures of brain microvessel endothelial cells proved to be a challenge, Ron arranged a meeting with Professor William "Bill" Pardridge from the UCLA School of Medicine in October of 1984. Professor Pardridge was one of a few prominent researchers in the area of drug delivery through the BBB at the time and he was in Lawrence (KS) to participate in a drug delivery conference dedicated to Professor Takeru Higuchi. Although a few examples of isolated brain microvessel endothelial cells and cultures of those cells appeared in the literature prior to 1984, the leads and contacts Professor Pardridge provided in the meeting were key in the eventual development of a primary cell culture system derived from bovine brain tissue.[143] Primary cultures of bovine brain microvessel endothelial cells (BBMEC) could be grown in culture dishes or on semi-permeable supports

and were exploited to understand nutrient and drug transport,[144-149] metabolism mechanisms,[150-154] and receptor expression.[155-157] These validating studies led to the use of this BBMEC model for subsequent mechanistic and structure-property relationship studies of drug transport across the BBB (see sections on **Prodrug Strategies for Therapeutic Peptides** and **Characterization of Drug-like Properties**). The interest in this work also prompted at least six review articles summarizing their accomplishments from 1987 to the last one in 1998.[158]

When Dr. Ismael J. Hidalgo joined Ron's research group in 1986 as a postdoctoral fellow, they pursued the elusive idea of developing a cell culture model of the intestinal mucosa. The "back story" for this pioneering work has been told by Ron in 2011.[138] Dr. Hidalgo identified several papers published in the 1970s and early 1980s by Professor Alain Zweibaum and colleagues at INSERM (Villejuif, France) describing the human colon adenocarcinoma Caco-2 cell line that spontaneously differentiates into polarized, confluent cell monolayers with tight junctions in approximately 15–20 days.[159] When grown on a filter support, these cell monolayers display morphological, functional and enzymatic characteristics typifying the human intestinal mucosa.[160] As with the BBMEC model, validating studies on transport mechanisms were also conducted. For example, Dr. Hidalgo established that Caco-2 cell monolayers actively transported the bile acid taurocholate.[161] Then, Ron's laboratory and collaborators at The Upjohn Company (Kalamazoo, MI) used the Caco-2 cell model to evaluate whether the bile acid transporter can enhance the ability of renin-inhibitory peptides to penetrate the intestinal mucosa by synthesizing and testing peptide-cholic acid conjugates.[162] A similar "one-two punch" was used by exploiting the functional expression of a biotin (vitamin H) transporter, now known to be the sodium-dependent multivitamin transporter (SMVT or SLC5A6), in Caco-2 cells and the intestine to assess whether oral absorption of peptidic HIV-1 protease inhibitors could be enhanced through biotin-peptide conjugation.[163,164]

Such studies led to many subsequent applications of the Caco-2 cell and BBMEC models in Ron's laboratory to elucidate the structural features of peptides and peptidomimetics influencing their ability to cross cell membranes. The cell-based systems also have been used in Ron's laboratory to develop innovative prodrug strategies that result in enhanced cell membrane permeation of peptides with a particular focus on the importance of conformation of cyclic prodrugs of peptides on membrane permeation as discussed in **Prodrug Strategies for Therapeutic Peptides** and **Characterization of Drug-like Properties**.

These cell culture models have opened new paths of research and have had enormous impact on several areas within pharmaceutical sciences, more specifically within drug delivery research and drug discovery. The Caco-2 model is presently being used worldwide as a screening tool during drug discovery to compare putative drug candidates for their absorption potential and to eliminate drug candidates that are likely to fail in later development due to poor biopharmaceutical properties. These cell monolayer models therefore have become a very important decision making tool in the pharmaceutical industry resulting in improved accuracy in prioritizing new compounds at the discovery stage. Besides the intrinsic originality and quality of these studies, the contributions from Ron's laboratory literally created a new approach to drug discovery development where pharmaceutical scientists were willing to use cell culture models to study drug transport across biological barriers instead of animal, tissue, and isolated cell models. As a consequence of their collective Caco-2 work and its impact, Ron and Dr. Hidalgo shared a 2007 award from the Society for Biomolecular Sciences Polypops Foundation.

This is one area of Ron's research that fueled and benefitted from his intense dedication to education and shared learning. In addition to launching two short courses on cell lines and tissue culture in pharmaceutical research and development at KU in response to the outpouring of requests for acquiring these models, Ron was co-editor or series editor for two books on this topic.[165,166] He also organized and participated in three American Association of Pharmaceutical Scientists (AAPS)-sponsored short courses on cell culture systems in 1994, 1996, and 1998.

The above provides a brief summary and not an in-depth review of Ron's contributions over the past 32 years to the area of cell-based models for biological barriers to drug delivery. For more details about his publications in this area, please refer to the following website: http://pharmchem.ku.edu/ronald-borchardt-0.

Protein and Peptide Stability

When Ron was selected as Chairman of the Department of Pharmaceutical Chemistry at KU in 1983, he seized that opportunity to lead the department into the area of pharmaceutical biotechnology. That seminal decision lead to the establishment of a course in the department's graduate program which was focused on pharmaceutical biotechnology and also in the recruitment of new faculty members with research interests focused in this emerging area. Over the years, Ron's decision has radically transformed KU's Department of Pharmaceutical Chemistry, where today more than 70% of the faculty members perform research in this area, including the design, formulation, stabilization and analysis of protein pharmaceuticals and vaccines.

Instrumental to the evolution of pharmaceutical biotechnology education and research at KU was securing a NIH Training Grant in this area, which Ron successfully did in 1989. That Training Grant still exists in the department today. In fact it was recently renewed, which means it will continue to support pharmaceutical biotechnology graduate students at least until 2019. Thirty years of continuous support for this type of NIH Training Grant is very unusual and a significant accomplishment for the faculty members in KU's Department of Pharmaceutical Chemistry. An important aspect of this Training Grant is the requirement for graduate student trainees to accept 3-6 month industrial internships in biotechnology companies. These internships soon became an important part of training not only for the graduate students being supported by the Training Grant, but also for most of the graduate students in KU's Department of Pharmaceutical Chemistry. These industrial internships have opened the door to multiple collaborations between students, faculty members and industrial scientists and to future career paths for the department's graduate students.

With respect to Ron's research, his first publication in the area of pharmaceutical biotechnology dates back to 1989 when he authored a review paper with Dr. M.C. Manning entitled "Stability of Protein Pharmaceuticals".[167] The importance of this paper in the field is evident from the fact that it has been cited over 700 times as of August 2015.

The research interest of the Borchardt laboratory in peptide and protein stability began to increase in the early 1990s. The first research papers in this field from his laboratory, which were published in 1990, focused on deamidation and on the influence of peptide sequence on the deamidation of asparagine residues.[168,169] These papers became the first in a series of important papers addressing the kinetics of hydrolytic degradation

reactions in solution,[170] in polymers[171] and in the solid state,[172] and the effects of sequence,[170] secondary structure[173] and formulation variables[174] on these kinetics. Rate constants derived in these studies continue to guide researchers in their quest to identify hotspots for asparagine deamidation in therapeutic peptides and proteins.

In 1991, Ron expanded his research interests to cover mechanisms of peptide and protein oxidation, and a series of papers documented his prolific efforts in this area.[175,176] It was around this time, that a group of international students and postdocs in his laboratory decided to use the Thanksgiving Break for a road trip to New Orleans. This group included about half of the biotechnology researchers in Ron's laboratory at that time. Realizing the inexperience of the foreigners, and the potential dangers of a big American city, Ron not only rescheduled a group meeting originally planned for the day after Thanksgiving (!), but also quickly changed the topic of the meeting from a discussion of research progress to general travel advice and rules of conduct, especially on Bourbon Street. Everybody made it back safely and biotechnology research continued to evolve in the Borchardt research group.

In the pursuit of his research interests, Ron had the foresight to assemble teams of various faculty members, graduate students and postdoctoral fellows with complementary expertise to drive projects in areas like peptide and protein stability. Besides Ron, the other KU faculty members involved in these pharmaceutical biotechnology projects were Professors Richard Schowen, Christian Schöneich and Elizabeth Topp (now at Purdue University). Such collaborations resulted in a multi-year project on hydrolytic degradation pathways of peptides and proteins in polymer matrices and the solid state. In this project, the precise mechanism of racemization during asparagine deamidation was elucidated.[177] The collaboration of these faculty members, graduate students and postdoctoral fellows not only ensured competitive NIH funding, but also created a climate of intense exchange and development of ideas, which paved the way for many successful careers of young researchers and faculty members.

Mentoring young researchers was close to Ron's heart, and key to the success of the Department of Pharmaceutical Chemistry during his tenure as Chairman. The countless opportunities he outlined before his colleagues, e.g., scientific collaborations, new research areas, ideas for potential courses, short courses, and scientific inquiry, provided and continue to provide a fertile ground for scientific discovery in KU's Department of Pharmaceutical Chemistry. For example, today the Department of Pharmaceutical Chemistry is home to the Macromolecule and Vaccine Stabilization Center and the Kansas Vaccine Institute. The existence of these two Centers is a logical extension of what began with Ron's vision to establish pharmaceutical biotechnology in the Department of Pharmaceutical Chemistry at KU.

The above provides a brief summary and not an in-depth review of Ron's contributions over the past 32 years to the area of protein and peptide stability. For more details about his publications in this area, please refer to the following website: http://pharmchem.ku.edu/ronald-borchardt-0.

Characterization of Drug-like Properties

When Ron took over the responsibility as the Chair of the Department of Pharmaceutical Chemistry in 1983, he made a strategic decision to pivot his training and experience as well as his instincts as a medicinal chemist to address one of the most relevant questions in drug discovery and development of the time – "what does it take for a molecule with potent and selective biological activity to become a successful drug?" Therein lies the genius of this incredible scientist/teacher/mentor/faculty member/Department Chair! Too many times, scientists let their training and their strength in a specific area of science become their biggest limitation, and see the world through the glasses of their training. Ron took a very different approach. An approach that has been a hallmark of his long and illustrious career, and that is to step back from time to time, and reflect on the most relevant questions that are staring us in the face, and then attack the problem by applying one's own training and by bringing in new talents from different disciplines. The quote "For example, this career change… in pharmaceutical chemistry." (see **The Change to Pharmaceutical Chemistry** section) from Ron's commentary[138] expresses well this philosophy in his own words. Perhaps he does not realize this, but this approach of Ron's has been an inspiration to many of his students and junior colleagues, represented by some of the co-authors of this commentary, who have watched him from a distance as they are pursuing their careers in academia or industry and as they have made their own career transitions.

Coming back to the question Ron asked about the properties of a molecule that would make it a successful drug, Ron turned his attention to the two barriers that routinely prevent the drugs to reach where they are supposed to reach to achieve their therapeutic potential, i.e., intestinal mucosa that prevents orally administered drugs to reach systemic circulation, and BBB that prevents the drug designed to treat central nervous system diseases from reaching the brain tissue. He recognized the importance of designing drugs and formulations that can enable the drug to navigate across these barriers successfully. Ron's training and instincts as a medicinal chemist led him to look for simple in vitro tools to screen for compounds that can or cannot cross these barriers. He recognized that traditional in vivo approaches using animal models would be too slow for screening and too complex to understand the problems associated with poorly performing compounds, and proceeded to develop cell culture-based models of the BBB and intestinal mucosa by bringing in postdoctoral fellows as described in the **Practical Models for Biological Barriers to Drug Delivery** section. Using a typical "Borchardt approach", Ron recognized the potential importance of peptides and peptide-like compounds as an attractive chemical space for discovering new drug candidates, but also recognized the liabilities of these molecules with respect to stability and permeability across biological barriers such as BBB and intestinal mucosa. Hence, Ron undertook a significant effort in elucidating the physicochemical properties of peptides that affect their stability and permeability, and therefore their ability to be useful drugs. Ron's work in these areas is described below and in the **Prodrug Strategies for Therapeutic Peptides** section.

The work done in Ron's laboratory starting in the mid-1990s focused on elucidating the "structure-transport relationships" for peptides and peptide-like compounds (also referred to as peptidomimetics). The model biological model systems used in these studies included cell culture models and *in situ* perfusion models of the intestinal mucosa and the BBB (see the Practical Models for Biological Barriers to Drug Delivery section). The physicochemical and biological properties studied by Ron's group over about a 10 year period included the following: (i) the effect of beta-turn structures on passive diffusion of peptides and peptidomimetics through the intestinal mucosa and the BBB;[178-180] (ii) the effect of hydrogen bonding potential on passive diffusion and passive diffusion modified by efflux transporters of peptides and peptidomimetics through the intestinal mucosa

and the BBB;[181-186] (iii) the effect of structural features of peptides and peptidomimetics on substrate activity for the peptide transporter in the intestinal mucosa;[187-191] and (iv) the effect of structural features, particularly size and charge, of peptides and peptidomimetics on their permeation via the paracellular route across the intestinal mucosa.[192] The results of these studies are described in several review articles.[193-196] The advances made by Ron's group in this area were made possible through longstanding and productive collaborations with his fellow KU faculty members including Professors Teruna Siahaan, Jeffrey Aube (now at the University of North Carolina) and David Vander Velde (now at CalTech), as well as Professors Ralph Hirschman and Amos B. Smith at the University of Pennsylvania, Drs. Philip Burton and Norman Ho at the Upjohn Company and Drs. Philip L. Smith and Chao-Pin Lee at SmithKline Beecham Pharmaceuticals.

Ron's work on "identifying, screening for, and improving drug-like properties" since the 1980s has had an enormous impact throughout the pharmaceutical and biotechnology industry. Arguably, even bigger impact on the industry and science of drug development in the area of "instilling drug-like property into drug candidates" has been through Ron's contributions as an educator. Ron has been a "preacher" to the "drug discovery and development community", and the central message of his "sermon" is "drug candidates are not high-affinity ligands, they must have drug-like properties". Ron has relentlessly conveyed the message that one must instill "drug-like properties" in drug candidates, and many of the authors of this commentary have either witnessed Ron "preaching" this "sermon" or have joined him at his invitation to help him in this mission. Ron's enormous work and equally enormous impact in this area is reflected in a large number of books that he has edited or co-edited,[197-201] and courses or workshops (sponsored by professional associations (e.g., AAPS), universities (e.g., Drew University), student-centered conferences (e.g., Globalization of Pharmaceutics Education Network), and pharmaceutical/biotechnology companies (e.g., on-site courses offered in the U.S.A. and Europe)) that he has organized, co-organized, and taught. The courses organized by Ron and sponsored by Drew University that focused on "designing drugs with optimal in vivo activity after oral administration" and "designing drugs with optimal blood-brain barrier permeability" for nearly 10 successive years were so popular among pharmaceutical scientists, managers, and senior leaders that many applicants had to be turned down each year. Many of the authors of this commentary were invited by Ron to participate in these short courses, specifically, the Drew University short courses, and have witnessed the enormous impact Ron has had through these courses by training thousands of pharmaceutical scientists in the science and art of designing and developing drugs with optimum pharmaceutical properties. One of the authors of this commentary (Professor Thakker) has had the privilege to not only participate in many of the short courses and workshops organized by Ron, but also travel with him (and Professors Val Stella and Kim Brouwer) over 30 times to various companies (and groups of companies) across the U.S.A. and in Europe to teach the course on "designing drugs with optimal in vivo activity after oral administration" over a 10-year period. During those trips, one witnessed the masterful teacher at work. Ron showed his mastery at engaging his audience with humor, story-telling, artfully created visuals, and straight-talk. Those trips taught so much to his "touring team members" and will always have a special place in the hearts and minds of Ron's traveling teammates.

In addition to teaching the science of optimizing drug-like properties, Ron took the opportunity to teach his audiences the value of communication and teamwork across various drug discovery/development disciplines. In his inimitable style, Ron would chide the company scientists in the audience by telling them that often he ended up introducing the scientists in the medicinal chemistry or biology department of the company to their

colleagues in the formulation or drug metabolism/pharmacokinetics department. Ron would show slides depicting "silos" within discovery research, preclinical development, and clinical development; he would also show slides that depicted lack of interactive feedback between these silos, and label those as "Recipe for Failure!!!". He would have slides with a title like "Because of a Lack of Input from Development Scientists, Discovery Scientists Tended to Fall into "The High Affinity Trap", followed by slides showing Drug Discovery Paradigm of the Future. Unquestionably, through these teachings Ron has had an impact in drug discovery/development that is quite difficult to measure. All one can say is "the impact has been truly transformative".

The above provides a brief summary and not an in-depth review of Ron's contributions over the past 25 years to the area of characterization of drug-Like properties. For more details about his publications in this area, please refer to the following website: http://pharmchem.ku.edu/ronald-borchardt-0.

Prodrug Strategies for Therapeutic Peptides

Ron's research interests concerning prodrugs have been focused on improving the delivery of drug molecules across biological barriers such as the intestinal mucosa and the BBB.[202] A prodrug is a conjugate of a promoiety to a functional group of the drug via a cleavable bond (e.g., ester, amide). The formation of a prodrug transiently changes the physicochemical properties of the drug for improving solubility and/or cell membrane permeation through the intestinal mucosa and/or BBB. The idea is that the bond between the drug and promoiety can be cleaved by enzymatic and/or chemical reaction(s) to convert the prodrug to the drug after delivery to the site of action. As his work in other fields, Ron's research in the prodrug area is a beautiful reflection of his ability to go across disciplinary boundaries in finding solutions to contemporary pharmaceutical problems.

After moving to KU to become a faculty member, Ron and his graduate student Kent Amsberry took advantage of Ron's findings as a postdoctoral fellow at the NIH related to the lactonization rate acceleration by a "trimethyl lock"[6-10] and applied them to prodrug design. Specifically, they compared prodrugs of p-methoxyphenyl amine, model compound, using 3-(2'-(benzyloxy)-4',6'-dimethylphenyl)-3,3-dimethylpropionic acid (3-BDPA) and 2'-hydroxyhydrocinnamic acid (2'-HHCA) promoieties to prove that this "trimethyl lock" group affected the rate of release of the amine. It was shown that the rate of p-methoxyphenyl amine release from the 3-BDPA promoiety having the "trimethyl lock" was 25,000 times faster than from the parent 2'-HHCA promoiety without the "trimethyl lock".[203] Ron and colleagues then extended the "trimethyl lock" concept to a quinone promoiety, which is a redox-sensitive promoiety for lactonization, to convert the amine prodrugs to the drug.[204]

In another example of bringing in tools available in related disciplines to solve pharmaceutical problems, Ron' research group worked on understanding the effect that the conformation of delta-sleep-inducing peptide (DSIP) had on its ability to cross the BBB.[205] To accomplish this goal, they studied the conformation of DSIP using various biophysical methods (i.e., NMR, CD, FTIR, and fluorescence) and found that DSIP had a propensity to form type-I beta-turns at residues 2–5 and 6–9, suggesting that the conformation of DSIP could contribute to BBB permeation.[205] Using a conformationally-stable hexapeptide fragment of DSIP, Ron's group systematically studied the effect of conformation on membrane permeation using linear and cyclic peptides.[178] They discovered that the cyclic hexapeptide had a faster cell membrane permeation rate than the linear hexapeptide;

furthermore, the cyclic hexapeptide had a more well-defined structure than the linear peptides as determined by various biophysical methods (i.e., NMR, molecular dynamics simulations).[178] This study suggested that stabilization of peptide conformation by forming cyclic peptides could enhance peptide transport through cell membranes.

Although cyclic peptides have better cell membrane permeation than linear peptides, the formation of a cyclic peptide from a linear peptide can alter the biological activity of the linear peptide. Therefore, there was a need to find a way to form cyclic peptides temporarily. To solve this problem, the Borchardt group investigated the formation of cyclic peptide prodrugs that would temporarily stabilize the peptide conformation and, at the same time, change the physicochemical properties of the peptide to favor cell membrane permeation.[202] The idea was that the cyclic peptide prodrugs could be converted to parent peptides after the transport process. Ron and his collaborators developed and studied the cyclic prodrugs of opioid peptides using different promoieties, including "trimethyl lock" phenyl propionic acid, coumarinic acid, acyloxyalkoxy, and oxymethyl-modified coumarinic acid (OMCA) promoieties.[202,206,207] The cyclic peptide prodrugs were constructed by linking the peptide N-terminus to the promoiety via an amide bond and the C-terminus to the promoiety via an ester bond. The subsequent improvement in membrane permeability is due to the stabilized conformation of cyclic peptide prodrug that reduces hydrogen bonding potential, increases hydrophobicity, reduces charges, and increases metabolic stability against exo- and endopeptidases. The cyclic peptide prodrugs can also be converted to the parent peptides by enzymatic reaction followed by rapid chemical reaction.

In the prodrug area, the Borchardt group has had a major impact on improving oral absorption and brain delivery of small molecules, including peptides, and peptidomimetics and achieving a good understanding of factors important to controlling delivery properties.[202] Reflected in these advances was also Ron's ability to build teams of collaborators from related disciplines. Especially worth mentioning was his long-standing and productive collaborations with Ron's KU faculty colleagues Professor Teruna Siahaan and David Vander Velde (now at CalTech). Ron's former postdoctoral fellow, Professor Binghe Wang of Georgia State University, also continued his collaboration in the prodrug area with Ron for a number of years after leaving his laboratory. Other investigators have also applied the "trimethyl lock" promoiety and similar concepts to make prodrugs of anticancer agents (e.g., daunorubicin, ganciclovir, taxol) as well as fluorogenic probes.[11] Ron's group and others have utilized the cyclic peptide prodrug concept to improve oral delivery of antithrombic agents (RGD peptides and peptidomimetics).[208-212] Finally, the "trimethyl lock" concept has also been utilized in cleavable linkers or protecting groups in the solid-phase synthesis of peptides and oligonucleotides.[11]

The above provides a brief summary and not an in-depth review of Ron's contributions over the past 25 years to the area of prodrugs of therapeutic peptides. For more details about his publications in this area, please refer to the following website: http://pharmchem.ku.edu/ronald-borchardt-0.

National and International Recognition for Research

The sheer number and quality of Ron's contributions are a testament to his deserving accolades. Over his 50-year career, Ron has published approximately 500 scientific papers in peer-reviewed journals, has authored or co-authored approximately 460 posters and podium presentations at national and international meetings, and

has presented approximately 180 invited talks of which about 40% were international. Ron's colleagues, both at home in the USA and throughout the world have frequently accorded him appreciative recognition for the quality and quantity of his research work. Most recently, in 2008, the Academy of Pharmaceutical Sciences and Technology-Japan (APSTJ) appointed him an International Fellow for his lifetime contributions to the pharmaceutical sciences. He was inducted into the American Chemical Society-Medicinal Chemistry Division Hall of Fame in 2007 in recognition of his lifetime contributions to the field of medicinal chemistry. In the same year, Ron and Dr. Ismael Hidalgo shared the Society for Biomolecular Sciences Polypops Foundation Award for the seminal discovery and development of Caco-2 cells as a model for the intestinal mucosa. Ron was the recipient in 2003 of the Smissman-Bristol-Myers Squibb Award in Medicinal Chemistry, given by the Medicinal Chemistry Division of the American Chemical Society (ACS) for his research contributions to the field of medicinal chemistry. Also in 2003, the American Pharmacists Association chose Ron to receive its most prestigious scientific award, the Takeru Higuchi Research Prize, for his lifetime research and educational contributions to the pharmaceutical sciences. The same association had in 2001 given Ron its Research Achievement Award in the Pharmaceutical Sciences for research contributions to that field. Ron's lifetime research and educational contributions to the pharmaceutical sciences earned him in 1999 the most prestigious award given by the International Pharmaceutical Federation, the Host-Madsen Medal, presented by its Board of Pharmaceutical Sciences. The Volwiler Research Achievement Award, the most prestigious award of the American Association of Colleges of Pharmacy (AACP), went to Ron in 1998 for his lifetime research and educational contributions to the pharmaceutical sciences. Ron's research contributions to the field of biotechnology brought him in 1997 the Paul Dawson Biotechnology Award from the AACP. In the same year, the AAPS selected Ron, in recognition of his lifetime research and educational contributions to the pharmaceutical sciences, to receive the most prestigious award given by AAPS, the Distinguished Pharmaceutical Scientist Award. Ron was elected Fellow of the American Association for the Advancement of Science (AAAS) in 1995. In 1994 Ron's research contributions to the field of medicinal chemistry brought him the Research Achievement Award in Medicinal Chemistry and Natural Products Chemistry from the AAPS. The same body, AAPS, had given Ron the Research Achievement Award in Biotechnology in 1993 for research contributions to the field of biotechnology. Also in 1993 Ron was the recipient of the Takeru and Aya Higuchi Memorial Award of the APSTJ. This award was given to him for his research contributions to the field of pharmaceutical chemistry. It is the most prestigious award given by APSTJ in the field of pharmaceutical chemistry. Ron was elected Fellow of the AAPS (1988). Ron was the 1983 winner of the Dolph Simons Sr. Award for research achievement in the biomedical sciences. For his contributions to biochemistry, Ron was given the Sato Memorial International Award from the Pharmaceutical Society of Japan in 1981.

In addition to these prizes and awards, Ron has received honorary doctorates from the Danish University of Pharmaceutical Sciences, Copenhagen, Denmark (2002), the Katholieke Universiteit, Leuven, Belgium (2004) and from Uppsala University, Uppsala, Sweden (2006).

Mentor of Graduate Students and Postdoctoral Fellows

Ron's research groups were vital, exciting to work in, intellectually nurturing, and professionally productive. Over the years, 19 Master's students, 62 Ph.D. students, 63 postdoctoral students, and 24 visiting scientists from around the world worked in Ron's laboratory. These individuals were associated with the Departments of

Biochemistry, Medicinal Chemistry or Pharmaceutical Chemistry at KU, or with the Danish University of Pharmaceutical Sciences, Copenhagen, Denmark or Uppsala University in Uppsala, Sweden.

Ron made use of an exceedingly effective means of directing and advising doctoral research students, a means that left each student with an approach to research that was optimal for time and resource management, for exercising good judgment in choosing among alternative research pathways, and which assured that important matters were not neglected or forgotten in assembling the experimental support for papers in preparation.

When new students joined the group, they and Ron in private conversation worked out a plan for the doctoral dissertation, i.e., the questions to be answered and at least a first few steps in the direction the experimentation should take. The students then went off to read and begin to develop what will in the end form the table of contents of the doctoral dissertation. At group meetings, they would soon present a draft table of contents in which they will have divided the overall problem into a strategic collection of parts, each commonly forming a coherent whole that will become a chapter in the dissertation, and that appears to represent an orderly approach to the overall problem. Good feedback was always offered by attendees at every group meeting; Ron continuously modeled how to correct or criticize in a collegial and good-humored way, so that a tone of friendliness and helpfulness prevailed. There was also a deliberate tone of egalitarianism: Ron never spoke to senior people with any greater (or lesser) courtesy or respect than he used with the newest students.

The same respect, courtesy, and collegiality prevailed in the laboratory where the students and postdoctoral coworkers pursued the experimental and sometimes computational aspects of the work. They all understood and appreciated how these qualities (which one would suspect in many cases were aspects of Professor Smissman's practices that Ron had explicitly or implicitly taken over into his own approaches) create a highly productive group with members who lead a pleasant daily life and form in many cases lifelong friendships.

As students progressed through the graduate program and moved toward "writing up" and receiving their degrees, their draft table of contents became an invaluable tool for time and resource management, and offered many opportunities for instilling and elaborating a culture of timely publication in the correct journals. It is a vital educational necessity to bring maturing young scientists into this culture and to equip them with decision - making tools that enable a thoughtful assessment of their research and what to do about it at any arbitrary time, of what direction to go next, how to finish up a paper for publication with no dangling unanswered questions, and many other potential pitfalls.

In addition to the above, Ron always encouraged all coworkers at every level to seize all opportunities to present their scientific work, either orally or in print, thus simultaneously "spreading the word" about what they had found, and also honing their skills in scientific communication. Although Ron's travel schedule was truly hard to believe, in terms of the frequency of travel and the intensity of the work he managed to force into every spare second of a trip, the fact was that no coworker of his ever lacked for his dedicated and thoughtful attention at any point – while working on the draft of a manuscript, preparing an oral presentation or a poster presentation. For graduate students, there was no choice: Ron saw to it that he heard rehearsals of talks, went over presentation slides or went over posters, provided detailed critiques, and was there to hear or go over the corrected version. For postdocs or colleagues, he was available if and as desired.

Mentor of Faculty Colleagues

Ron has always taken an interest in the academic fortunes of his colleagues, and has given valuable advice and encouragement. If their later success is any measure of his influence, it has certainly been good.

- Professor Kenneth Audus, a postdoctoral fellow with Ron who was critical in the development of a cell-culture model for the BBB, joined the faculty of the Department of Pharmaceutical Chemistry at KU in 1986 and rose through the academic ranks to become a Full Professor in 1996 and then Chair of the Department in 1998. Ken is also a Professor of Molecular & Integrative Physiology at KU Medical Center in Kansas City and became Dean of the School of Pharmacy in April of 2004. He is a Fellow of AAPS and he has been recognized as an AACP Teacher of the Year and for Excellence in Undergraduate Teaching of Pharmaceutical Chemistry at KU.
- Professor Christian Schöneich, while a postdoctoral coworker of Professor George Wilson and Ron, began his studies of oxidation reactions in proteins and peptides. As a young faculty member whose own graduate education had been completed in the rather different German academic system, Christian had to make some adaptations to the American and indeed KU systems, and Ron surely helped. Christian is now the Chair of the Department of Pharmaceutical Chemistry at KU and holds the Takeru Higuchi Distinguished Professorship of Bioanalytical Chemistry.
- Professor Teruna Siahaan took bachelor's and master's level degrees in chemistry at the University of Indonesia and obtained his Ph.D. in organic chemistry with Professor Robert Bates at the University of Arizona, followed by postdoctoral study with Professor Bruce Lipshutz in the Department of Chemistry and Chemical Biology of the University of California at Santa Barbara. His work at KU, now as Professor of Pharmaceutical Chemistry, in the general areas of biotechnology, drug delivery, protein and peptide chemistry and biochemistry has been closely allied with that of Ron, who is surely gratified that the work has won Teruna admiring notice, as the following recognition attests: PhRMA (Pharmaceutical Research and Manufacturers Association) Foundation Award in Excellence in Pharmaceutics, 2014; Research and Academic Mentor of the Year, Office for Diversity in Science Training, KU, 2013; Clarence Karcher Lecturer, University of Oklahoma, 2005; Fellow of AAPS, 2002; Eurand Honorable Mention Award, Controlled Release Society, 2002; Pfizer Research Scholar Award (2002–2004); Self Faculty Scholar, KU (2001–2004).
- Professor Elizabeth Murphy (Liz) Topp, while ascending the professorial ranks in the Department of Pharmaceutical Chemistry at KU, devoted a good part of her research program on peptide and protein stability, particularly in amorphous solid states, to collaborations with Ron. She is currently the Dane O. Kildsig Chair and Department Head of the Department of Industrial and Physical Pharmacy at Purdue University. While still at KU, Liz won the Madison & Lila Self Graduate Mentor Award twice, and was named "Teacher of the Year" by AACP. At Purdue, she holds an endowed professorship and won the Seeds for Success Award, the AAPS Fellowship, and has been named an Academic Leadership Fellow.

Global Teacher

At the very beginning of his professorial career, Ron proved to combine excellence in research with a very marked talent for teaching. One ought to note that this combination is not as rare in fact as it may be thought in the popular imagination; commonly good teachers are good researchers and bad teachers are bad researchers.

The phenomenal difference with Ron is that he is not just good at both activities, but he is extraordinarily good at both. In 1980, the year after he was promoted to full professor of biochemistry, Ron won the Mortar Board Outstanding Educator Award, a student-sponsored award that is given to faculty members for "their dedication to KU and positive influence on students both academically and personally." Most of us feel that when such recognition comes directly from students, as is the case here, it is especially significant. His excellence in teaching continued throughout his career at KU as evidence by his selection in 1997 to receive the Louis Byrd Graduate Educator Award and his selection in 2005 to receive the Chancellors Club Career Teaching Award. The Chancellors Club Career Teaching Award is the most prestigious teaching award given to faculty members at KU.

Ron often managed to combine his talents in teaching and research in very unique and effective ways. Starting in 1994, as he was developing his research program into one (in the Department of Pharmaceutical Chemistry) incorporating drug delivery as a main theme, he launched two short courses, one on cell lines and tissue culture in pharmaceutical research and development, the other on designing drugs with optimal in-vivo activity after oral administration. These courses were given in circumstances, often at meetings of professional associations, so that the attendance of academics, students, and professional practitioners could be expected. This led to a very effective evangelization of the gospel Ron was promoting. These efforts were continued well into the 21st Century. For example, the oral-administration course was given on-site at pharmaceutical firms throughout the USA and in Europe (see **Characterization of Drug-like Properties** section) from 2000-2008.

University Administrator

A certain number of us initially sneer at the idea of making administrative contributions until something intervenes: we need something badly and a creative administrator steps into the breach, or a good friend becomes an active administrator and models how it can be done correctly and usefully. In Ron's case he must have been offered many, many such opportunities at KU. He seems to have tried out only the Directorship of the Center for Biomedical Research (7 years), the Chair of Pharmaceutical Chemistry (15 years), and Acting Dean of the School of Pharmacy (2 years). Ron says these were "test drives" and that he "chose to dedicate my life to teaching, mentoring, and research." He has certainly had a full life of his chosen emphases, but it is hard to conceive of anyone else who would consider a total of 24 years to be a test drive!

International Graduate Education: GPEN, the Globalization of Pharmaceutics Education Network

During the 1990s, Ron was as busy at consulting and advisory activities for the pharmaceutical industry as he had been nearly all his professional life: since 1975, he consulted for over 80 pharmaceutical companies and lectured at over 500 universities, research institutes, and pharmaceutical and biotechnology companies around the world. These activities doubtless provided him with a privileged viewpoint from which to observe the effects of conversion of large parts of the industry to international firms with movements of persons and information from place to place on a gigantic scale, in short the globalization of the industry. As Dean Kenneth Audus, has said, "Professor Borchardt recognized that the pharmaceutical sciences, and the industry and academia it served, was global. Moreover, students from institutions like KU would be working at and interacting with colleagues around the world throughout their careers in the pharmaceutical sciences. Therefore, as part of their

graduate education, he pursued the idea that students should be exposed to the international science and culture of the other top pharmaceutics programs in the world."

To see where this idea has gone, the reader should go to http://pharmchem.ku.edu/globalization-pharmaceutics-education-network-gpen. There one learns that GPEN, Inc., has conducted biennial meetings since 1996 in the United States (GPEN1996, University of Kansas) in Switzerland (GPEN1998, ETH-Zurich), Sweden (GPEN2000, Uppsala University) , United States (GPEN2002, University of Michigan), Japan (GPEN2004, Kyoto University), United States (GPEN2006, University of Kansas), Belgium (GPEN2008, KU Leuven), United States (GPEN2010, University of North Carolina), Australia (GPEN2012, Monash University), and Finland (GPEN2014, University of Helsinki)). A Board of Directors of which Dean and Professor Ken Audus is Chair manages this organization. Of the meetings, Audus says, "GPEN meetings are organized in entirety by graduate students of the hosting University. The meeting format includes a keynote address by a prominent scientist, scientific presentations and posters by graduate students, short courses by faculty, and social events that help introduce students and faculty attendees to the host country's culture. GPEN encourages the pharmaceutical industry to attend, provides support for participation by all of the 52 member schools, and actively endorses research exchanges between and among all of the institutions and their pharmaceutics programs. Professor Borchardt is a visionary in graduate education and training particularly with respect to the global needs of the pharmaceutical sciences." It is through these niche meetings that many graduate students have been able to make the necessary links with faculty members and industrial representatives around the globe leading to excellent future employment opportunities.

Sometimes people speak of "an idea whose time has come." There must be extremely few examples as clear as this one.

Editor of Books and Journals

It is a cliché to say that science requires absolutely that its results and the ideas that are used for interpreting them be made available to one's colleagues world-wide. Since the 18th century, a more and more complex set of means for dissemination of scientific information has developed, currently increasingly emphasizing the internet and electronic communication, but by and large in the chemical and biological sciences still tied to the printing of journals and books of the traditional kind. It is also expected by authors and demanded by readers that the publishers of journals and books will subject the individual units of publication, such as a chapter or a paper, to some form of peer review. The more rigorous the peer review, the higher will rise the respect and prestige that the journal or book and the enterprise that sees them into print and distribution also will rise. Staff members undertake some of this work, but to an enormous extent, volunteers from the ranks of practicing scientists donate their time and effort to seeing that we all have the opportunity to publish our work.

Ron has been an exemplary scientific citizen in this regard. He has at the present time been serving as Editor-in-Chief of the Journal of Pharmaceutical Sciences for 14 years. Prior to assuming the position of Editor-in-Chief, Ron served for 5 years as Associate Editor of the Journal of Pharmaceutical Sciences, 3 years as Associate Editor of the Journal of Peptide Science, and 2 years as Biotechnology Editor of the AAPS Journal.

Ron has also made a particularly significant contribution of a sort that often goes unnoticed i.e. editing of books and book series that come to be trusted sources of information. Between 1976 and 2007, he and his co-Editors brought out collections of expert reviews in books dealing with the chemistry and biochemistry of Ado-Met dependent transmethylations,[213-215] drug delivery,[216] cell culture and tissue models for assessing drug absorption,[165,166] characterization of drug-like properties, [197-199]and prodrugs.[200,201] In addition to editing these ten books, Ron has also served as Series Editor for 14 volumes of Pharmaceutical Biotechnology (Plenum Press) and 9 volumes of Biotechnology: Pharmaceutical Aspects (AAPS Press).

Consequential Consultation and Entrepreneurship

Ron has always found the pharmaceutical industry to have a powerful interest in receiving his advice as a consultant (from 1971 through the present, on more than 80 consultantship appointments), and as a member of advisory boards (from 1992 through the present, with over 30 appointments). These rosters of firms around the world reflect nearly the entirety of what might be called the most highly respected of the “pharma elite”.

On at least one occasion, Ron has dipped more deeply into the client’s activities than just offering suggestions. He was drawn into the work of Proteolix Pharmaceuticals on inhibitors of the 2S-proteasome, a large molecular machine of the cell that removes cellular detritus, proteins that are no longer useful and therefore have been tagged by ubiquitin to identify them as waste. An inhibitor of the proteasome causes it to cease catalyzing the destruction of tagged proteins, and the latter accumulate in the cell to the point that apoptosis or programmed cell death occurs. If this occurs sufficiently frequently in tumor cells, the inhibitor should be an anti-cancer agent. This proves to be the case with multiple myeloma when the inhibitor is carfilzomib (Kyprolis®), a Proteolix compound co-invented by Ron and now manufactured and distributed by Amgen, Inc. With the discovery of carfilzomib, patients with multiple myeloma now have another treatment option.

In 1997, Ron collaborated with Professor Valentino Stella, Professor Gunda Georg, Dr. Roger Rajewski and Dr. Osborne S. Wong to form ProQuest Pharmaceuticals. ProQuest's core technologies included patented prodrug strategies for increasing the cell permeation of therapeutic peptides, which came from Ron's laboratory, and patented prodrug strategies for enhancing the solubility of insoluble organic-based drugs, which came from Professors Stella's and Georg's laboratories. In 2000, Proquest licensed its lead compound (fospropofol) to Guilford Pharmaceuticals for preclinical and clinical development. In 2004, Guilford purchased ProQuest Pharmaceuticals outright in order to have full control over the clinical development and commercialization of fospropofol. LUSEDRA™ (fospropofol) was approved by the US Food and drug administration in 2008 for procedural sedation.

Ron and Pam Moving Forward

Ron’s exceptional academic career is balanced by his personal successes, the first being his almost 50-year marriage to wife, Pam. He is the first to note that Pam should be given full credit for raising and mentoring their three children in Lawrence while he spent much of his time in his office and laboratory at the university or traveling nationally and internationally. Not surprising, is that each child is successful in his and her own right. Scott, the eldest, is a Managing Director at PricewaterhouseCoopers, LLC, in Boston, MA, where he lives with his

wife, Julie, and their three children, Noelle, Nick, and Catherine. Paul resides in Lawrence where he works as the Tax and Compliance Reporting Officer at the Kansas University Endowment Association. His wife, Susan, who helps raise their son, Max, is a learning assistant for KU Athletics and teaches online English courses. Kelly, the youngest, has recently moved back to Lawrence after accepting a position as a Nurse Education Specialist with Children's Mercy Hospital in Kansas City, MO. Her husband, Phil, a former graduate student of Professor Richard Schowen, is a scientist at Zoetis, Inc. in Kalamazoo, MI.

Though Ron and Pam have lived in Lawrence, KS, for almost 45 years, they still cheer for the UW sports teams and the Green Bay Packers. The couple does have divided allegiances, however, during basketball season, as decades-long season ticket holders, they cheer for the KU basketball team, a focus of their winter and spring free time. While Pam travels with Ron to his various conferences, their most enjoyable trips are often back home to Wisconsin to enjoy their lakeside family cottage, sharing that cottage with family and friends every summer. Both also enjoy cultivating their extensive gardens in Lawrence, maintaining a backyard the Lawrence Journal-World newspaper called "a whimsical, picturesque, woodland habitat that's an absolute joy to behold" in a feature on their gardens.

The Borchardts also enjoy giving back to the universities that have given them so much. Ron and Pam, as well as their children, have all set up scholarships to support others in pursuit of their academic dreams. The Borchardts give back to UW through the Ronald T. and Pamela K. Borchardt Scholarships for Pharm. D. students. At KU, all the families contribute to various funds including the Borchardt Family Scholarship for Graduate Study in the Beach Center on Disability, the Borchardt Family Tax Scholarship in the School of Business, and the Borchardt Family Basic Pharmaceutical Sciences Award and Scholarship in the School of Pharmacy.

The KU community has always been supportive of Ron's efforts, and he and his family members have flourished because of it. The family currently holds a total of eleven degrees from KU. Ron's extended family, his approximately 170 graduate students, postdoctoral fellows, and visiting scientists, bring him a great deal of pride as well. Ron has said that it is his job to teach his students "not just how to get to the five-yard line" but how to score a touchdown. That so many of them have gone on to score that game-winning touchdown, in academia, industry and entrepreneurial pursuits, remains one of his greatest legacies.

Looking back on his career, Ron says he feels extremely fortunate to have had the opportunity to pursue his passion for research and teaching at KU. Having received direction and mentoring from the forward thinking minds of Professors Smissman and Higuchi while at the university, Ron now trusts that his colleagues, many of whom studied with him, will continue to provide the stability and direction to keep the Department of Pharmaceutical Chemistry and the School of Pharmacy at the university thriving.

In recognition of Ron's roles as a teacher, mentor and scientist, KU has created the Ronald T. Borchardt Distinguished Professorship in Pharmaceutical Chemistry. Notably, Ron's former graduate students, postdoctoral fellows, colleagues and friends in recognition of his contributions to their lives contributed most of the funding for this endowed distinguished professorship.

Ron is a man of many titles and accolades. However, the best of these may be ahead of him. On August 2, 2015, he transitioned into his new position as Distinguished Professor Emeritus of Pharmaceutical Chemistry at KU. Despite this new title, he will continue to be professionally active. In addition to maintaining his role as Editor-in-Chief of the Journal of Pharmaceutical Sciences, Ron will also continue to be involved in the leadership of GPEN, and to serve on several Scientific Advisory Boards and to provide consultation to pharmaceutical and biotechnology companies world-wide.

With perhaps some more personal time ahead, many have made suggestions for how Ron should spend that time: travel, family visits, landscaping, lake trips, or even as his sister suggests, engaging that creative part of his brain to learn a new language. Whatever he pursues in the next phase, we, as his friends, family, academic children and colleagues, can say one thing for certain: he will do it his way.

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